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(57) Abstract

The present invention is concerned with pharmaceutical compositions comprising a carrier and as first active ingredient an atypical antipsychotic agent (I) and as second active ingredient an acetylcholinesterase inhibitor (II), each in an amount producing a therapeutically beneficial effect in patients suffering from psychosis, or Alzheimer's disease or related dementias. Said therapeutically beneficial effect can be a synergistic effect on the cognitive functioning of patients suffering from Alzheimer's disease or related dementias or the prevention of the further deterioration of cognition in said patients, or the reduction of adverse effects associated with the one of the active ingredients by the other of the active ingredients.

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THERAPY FOR IMPROVING COGNITION

The present invention is concerned with pharmaceutical compositions comprising a carrier and as first active ingredient an atypical antipsychotic agent (I) and as second active ingredient an acetylcholinesterase inhibitor (II), each in an amount producing a therapeutically beneficial effect in patients suffering from psychosis, or Alzheimer's disease or related dementias. Said therapeutically beneficial effect can be a synergistic effect on the cognitive functioning of patients suffering from Alzheimer's disease or related dementias, or the prevention of the further deterioration of cognition in said patients, or the reduction of adverse effects associated with the one of the active ingredients by the other of the active ingredients.

Of particular interest is the use of an atypical antipsychotic agent (I) for the preparation of a medicament for reducing adverse effects associated with acetylcholinesterase inhibitors (II) in patients suffering from Alzheimer's disease or related dementias, such as nausea, vomiting, sweating, restlessness and insomnia. Especially interesting is the use of an atypical antipsychotic agent (I) for the preparation of a medicament for improving sleep in patients suffering from Alzheimer's disease or related dementias while being treated with acetylcholinesterase inhibitors (II).

The present invention is concerned with a pharmaceutical composition comprising a carrier and as first active ingredient an atypical antipsychotic agent (I) and as second active ingredient an acetylcholinesterase inhibitor (II), each in an amount producing a therapeutically beneficial effect in patients suffering from psychosis, or Alzheimer's disease or related dementias. Said therapeutically beneficial effect can be a synergistic effect on the cognitive functioning of patients suffering from Alzheimer's disease or related dementias, or the prevention of the further deterioration of cognition in said patients, or the reduction of adverse effects associated with the one of the active ingredients by the other of the active ingredients.

The atypical antipsychotic (I) is selected from risperidone, 9-hydroxyrisperidone or a C_{10-20} alkanoic acid ester thereof, olanzapine, quetiapine, iloperidone or ziprasidone, and the acetylcholinesterase inhibitor (II) is selected from galantamine, rivastigmine or donepezil, or therapeutically active acid addition salt form of any of the foregoing. Said salts comprise salt forms which the active ingredients (I) and (II) are able to form with appropriate acids, such as, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid; sulfuric; nitric; phosphoric and the like acids; or

organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic, malonic, succinic, maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, *p*-toluenesulfonic, cyclamic, salicylic, *p*-amino-salicylic, pamoic and the like acids. For example, galantamine may conveniently be used as the (1:1) hydrobromide salt.

C_{10-20}alkanoic acids are selected from the group consisting of decanoic (capric), undecanoic, dodecanoic (lauric), tridecanoic, tetradecanoic (myristic), pentadecanoic, hexadecanoic (palmitic), heptadecanoic, octadecanoic (stearic), nonadecanoic and eicosanoic acid. Due to their limited aqueous solubility, it was generally believed that the esters had to be suspended into oils. The ester having a C_{15} (pentadecyl) chain and the active ingredient corresponding thereto being the 9-hydroxyrisperidone palmitate ester was found to be the superior ester from a pharmacokinetic, as well as from a tolerance point of view.

Preferably, the amount of each of the active ingredients is equal to or less than that which is approved in monotherapy with said active ingredient.

Most preferred are compositions wherein the atypical antipsychotic (I) is risperidone and the acetylcholinesterase inhibitor (II) is galantamine, in particular as galantamine hydrobromide. In said compositions, the amount of risperidone is 0.5, 1, 2, 4, or 6 mg and that of galantamine (as base) is 8, 16, 24 or 32 mg per dosage form.

The present invention also relates to products containing as first active ingredient an atypical antipsychotic agent (I) and as second active ingredient an acetylcholinesterase inhibitor (II), as combined preparations for simultaneous, separate or sequential use in the treatment of patients suffering from psychosis, Alzheimer's disease or related dementias.

The present invention also concerns the use of an acetylcholinesterase inhibitor (II) for the preparation of a medicament for enhancing the effect of an atypical antipsychotic agent (I) on cognition in patients suffering from psychosis.

Conversely, the present invention also concerns the use of an atypical antipsychotic agent (I) for the preparation of a medicament for enhancing the effect of an acetylcholinesterase inhibitor (II) on cognition in patients suffering from Alzheimer's disease or related dementias.

Additionally, the present invention concerns the use of an atypical antipsychotic agent (I) for the preparation of a medicament for reducing adverse effects associated with acetylcholinesterase inhibitors (II) in patients suffering from Alzheimer's disease or related dementias. Said adverse effect can be nausea, vomiting, sweating, restlessness or insomnia. Especially interesting is the use of an atypical antipsychotic agent (I) for the preparation of a medicament for improving sleep in patients suffering from Alzheimer's disease or related dementias while being treated with acetylcholinesterase inhibitors (II).

Finally, the present invention also concerns the use of an acetylcholinesterase inhibitor (II) for the preparation of a medicament for reducing adverse effects associated with atypical antipsychotic agents (I) in patients suffering from psychoses. Said the adverse effect can be extrapyramidal syndrome or tardive dyskinesia.

In all the preceding uses the atypical antipsychotic (I) is preferably risperidone and the acetylcholinesterase inhibitor (II) is preferably galantamine, in particular the (1:1) hydrobromide.

Claims

1. A pharmaceutical composition comprising a carrier and as first active ingredient an atypical antipsychotic agent (I) and as second active ingredient an acetylcholinesterase inhibitor (II), each in an amount producing a therapeutically beneficial effect in patients suffering from psychosis, Alzheimer's disease or related dementias.

2. A composition according to claim 1 wherein said therapeutically beneficial effect is a synergistic effect on the cognitive functioning of patients suffering from Alzheimer's disease or related dementias, or the prevention of the further deterioration of cognition in said patients, or the reduction of adverse effects associated with the one of the active ingredients by the other of the active ingredients.

3. A composition according to claim 1 wherein the atypical antipsychotic (I) is selected from risperidone, 9-hydroxyrisperidone or a C_{10-20} alkanoic acid ester thereof, olanzapine, quetiapine, iloperidone or ziprasidone, and the acetylcholinesterase inhibitor (II) is selected from galantamine, rivastigmine or donepezil.

4. A composition according to claim 3 wherein the amount of each of the active ingredients is equal to or less than that which is approved in monotherapy with said active ingredient.

5. A composition according to claim 3 wherein the atypical antipsychotic (I) is risperidone and the acetylcholinesterase inhibitor (II) is galantamine.

6. A composition according to claim 5 wherein the amount of risperidone is 0.5, 1, 2, 4, or 6 mg and that of galantamine (as base) is 8, 16, 24 or 32 mg per dosage form.

7. A product containing as first active ingredient an atypical antipsychotic agent (I) and as second active ingredient an acetylcholinesterase inhibitor (II), as a combined preparation for simultaneous, separate or sequential use in the treatment of patients suffering from psychosis, Alzheimer's disease or related dementias.

8. The use of an acetylcholinesterase inhibitor (II) for the preparation of a medicament for enhancing the effect of an atypical antipsychotic agent (I) on cognition in patients suffering from psychosis.

9. The use of an atypical antipsychotic agent (I) for the preparation of a medicament for enhancing the effect of an acetylcholinesterase inhibitor (II) on cognition in patients suffering from Alzheimer's disease or related dementias.

10. The use of an atypical antipsychotic agent (I) for the preparation of a medicament for reducing adverse effects associated with acetylcholinesterase inhibitors (II) in patients suffering from Alzheimer's disease or related dementias.

11. Use according to claim 10 wherein the adverse effect is nausea, vomiting, sweating, restlessness or insomnia.

12. The use of an acetylcholinesterase inhibitor (II) for the preparation of a medicament for reducing adverse effects associated with atypical antipsychotic agents (I) in patients suffering from psychoses.

13. Use according to claim 12 wherein the adverse effect is extrapyramidal syndrome or tardive dyskinesia.

14. Use according to any one of claims 8 to 13 wherein the atypical antipsychotic (I) is risperidone and the acetylcholinesterase inhibitor (II) is galantamine.